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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,571	10/11/2005	Barry Barton	PB60213	4768

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/552,571	BARTON ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *3-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 October 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election, with traverse, of Group I (claims 1-2) and further elect SEQ ID NO:1 directed to a *S. clavuligerus* microorganism comprising mutations, in the reply filed on 19 July 2007. Because no argument for the traversal was provided by applicant, thus the traversal is non-persuasive and the restriction is made final.

Claim Status

Claims 1-2 are pending. However, claims 3-12 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-2 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The new oath or declaration, having the signatures of all inventors, received on 11 October 2005 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 11 October 2005 consisting of 3 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a 371 of PCT/EP04/04001 (filed 04/13/2004) and from foreign application UNITED KINGDOM 0308696.4 (filed 04/15/2003). The instant application has been granted the benefit date, 15 April 2003, from foreign application UNITED KINGDOM 0308696.4.

Specification/ Drawings

The disclosure is objected to because of the following:

The specification contains sequence disclosures (Figure 3 and page 18) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.82(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequences are not included in the original sequence submission, a paper copy and a computer readable copy of the sequence Listing and a statement that the content of the paper and computer readable

copies are the same and were applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

A full response to this Office Action must include complete response to the requirement for a Sequence Listing. The detailed description of Figure 3, should be amended to include the proper SEQ ID NO for the sequence depicted in Figure 3.

The sequences on page 18, seem to represent polynucleotides for which no SEQ ID NO is been associated.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: “Enablement is not precluded by the necessity for some 'experimentation.'” Clearly, enablement of a claimed invention cannot be predicated on

the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

SCOPE OF THE INVENTION

The breadth of the claims encompasses a genus of *S. clavuligerus* microorganisms comprising (1) a disruption/deletion of *cvm6para* (SEQ ID NO:1) and (2) double mutants comprising a disruption/deletion of *cvm6para* and a disruption/deletion of another *cvm* or *cvmpara* gene wherein production of 5S clavams "is reduced" and clavulanic acid production is "at least maintained"

GUIDANCE & QUANTITY OF EXPERIMENTATION

The specification provides the following definitions: "'Reduced' as used herein means that the levels of 5S clavam produced by the microorganism of the invention are lower than the levels produced in the corresponding *S. clavuligerus* strain which has not

had the relevant open reading frames disrupted or deleted" (page 3, lines 18-20) and "'at least maintained' as used herein means that the level of clavulanic acid produced in the microorganism of the invention is the same or greater than that produced in the corresponding *S. clavuligerus* strain which has not had the relevant open reading frames disrupted or deleted. " (page 3, lines 24-27). The specification also indicates that "the corresponding *S. clavuligerus* is therefore the 'parent' strain into which the disrupted or deleted open reading frames were subsequently introduced to generate the microorganism of the invention." (page 3, lines 20-23, 27-29).

The instant specification states, "These results suggest that like cvm6 the cvm6par gene is required for efficient production of the 5S clavams. Disruption of cvm6par not only results in a reduction in clavams but also a simultaneous increase in clavulanic acid." (page 16, lines 6-8). The specification makes this conclusion based on experiments in which *S. clavuligerus cvm6par* mutant is grown on soy medium. Tahlan et al. (Antimicrobial Agents and Chemotherapy, Mar. 2004; 48(3): 930-939) indicate that the type of medium is important to both clavaulanic acid and 5S clavam production, "This study extends the work of Jensen et al. (20), who found that *S. clavuligerus ceaS*, *bls*, *pah2*, *cas2*, and *oat* mutants, when prepared individually, still retained some ability to produce clavulanic acid and *5S* clavam metabolites in complex soy medium but not in defined SA medium." (page 937, Discussion). There is nothing in the claims, regarding differential production of clavulanic acid and 5S clavams, based on media type.

Therefore, the examiner concludes that there is additional experimentation required to make and use the claimed microorganism having the recited limitations.

STATE OF THE ART

The state of the art teaches that *S. clavuligerus* comprising single and double mutants of *cvm6para* (SEQ ID NO:1) (also known as *orf6* and *OAT1*) are not a enabled for the organism as claimed. The particular elements of the instant claims which are not enabled are not related to the structure of the deletions or *S. clavuligerus* comprising such deletions. Rather, the portion of the claims which are not enabled are the limitations reciting wherein production of 5S clavams "is reduced" and clavulanic acid production is "at least maintained." Tahlan et al. (Antimicrobial Agents and Chemotherapy, Mar. 2004; 48(3): 930-939) refer to a paralogue of the ornithine acetyltransferase gene by the names *oat1* and *orf6.* Tahlan et al. teach, "generation of an oat1 mutant…[and investigated] clavulanic acid and clavam metabolite biosynthesis…[and were] surveyed by fermenting different oat1 mutants in soy and SA medium along with wild-type cured strains. After 72 h of growth, clavulanic acid production was between 28 to 86% and 14 to 87% in SA and soy medium, respectively, compared to wild-type strains. After 96 h of growth, even more variation in clavulanic acid production was observed in both media compared to the cured wild-type controls. In SA medium clavulanic acid production varied from 30 to 154% and in soy medium from 57 to 145% compared to the wild-type strain. No specific trend in *5S* clavam production was observed, and cephamycin production was unaffected in the *oat1*

mutants." (page 936, col. 1, Generation of an oat1 mutant). The examiner concludes that the *S. clavuligerus* comprising a single *cvm6para* mutant as taught by Tahlan et al. (whose research group includes two of the applicants, Susan Jensen and Annie Wong) does not meet the limitations reciting wherein production of 5S clavams "is reduced" and clavulanic acid production is "at least maintained" because the 5S clavams is "variable" and the production of clavulanic acid is "reduced" relative to wildtype for some conditions/timepoints. Furthermore, the double mutant *S. clavuligerus* comprising disruptions of both *cvm6para* and *cvm6* (also referred to as *oat2*) also is not enabled for limitations reciting wherein production of 5S clavams "is reduced" and clavulanic acid production is "at least maintained." Tahlan et al. teach, "After 72 h of growth, HPLC analyses revealed that clavulanic acid production by the double mutant was between 3 to 9% and 24 to 56% of wild-type levels, in SA and soy medium, respectively. A similar decrease in clavulanic acid production was also observed in the culture supernatants analyzed after 96 h of growth (Table 4). Again, there was a high degree of variation in the levels of *5S* clavam metabolites produced, and no specific trend was observed." (pages 936-937, Generation of an oat1 and oat2 double mutant).

In addition, Tahlan indicate that the type of medium is important to both clavaulanic acid and 5S clavam production, "This study extends the work of Jensen et al. (20), who found that *S. clavuligerus ceaS*, *bls*, *pah2*, *cas2*, and *oat* mutants, when prepared individually, still retained some ability to produce clavulanic acid and *5S* clavam metabolites in complex soy medium but not in defined SA medium." (page 937, Discussion). There is nothing in the claims, regarding differential protein expression,

based on media type. This is in direct contraction to the specification's asserted conclusion, “Disruption of cvm6par not only results in a reduction in clavams but also a simultaneous increase in clavulanic acid” (page 16, lines 6-8).

Accordingly, the microorganism *S. clavuligerus* comprising single and double mutants of *cvm6para* (SEQ ID NO:1) are highly variable in achieving a reduction of 5S clavam expressed and at least maintaining clavulanic acid production. Consequently, there is ample reason to conclude that there would be a high degree of unpredictability in the instantly claimed invention.

CONCLUSION

In conclusion, due to the differences between the guidance of the specification and the contrary teachings of the art, the examiner concludes there is an undue quantity of experimentation is require to make and use the invention.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free)?

/SDL/ Scott Long Patent Examiner, Art Unit 1633	/Janet L. Epps-Ford/ Primary Examiner, Art Unit 1633